The Journal of
Laryngology and Otology

(*Founded in* 1887 *by* MORELL MACKENZIE *and* NORRIS WOLFENDEN)

April 1966

GLANDULAR FEVER*

By T. M. L. PRICE (London)

THE disease alternatively called glandular fever and infectious mononucleosis presents some intriguing problems, among which are its powers of mimicry. Davidsohn in a report on the value of the Paul Bunnell test lists 26 different initial diagnoses in 63 patients subsequently found to have glandular fever (Davidsohn *et al.*, 1951). Another difficulty concerns the definition of the disease. What constitutes glandular fever? Is it one disease, or two, or many? Is a positive Paul Bunnell test necessary or not? It is accepted that the disease is infective, but no agent has ever been identified and transmission to animals and human volunteers has not been satisfactorily demonstrated. Indirect evidence suggests that the agent is probably a virus related to the myxo-viruses (Evans, 1960).

Several studies comparing cases with positive and negative Paul Bunnell tests have shown much the same state of affairs—that the clinical features are very similar though the serologically positive cases occur on the whole in an older age group and tend to be more severe, while the seronegative cases show a more diverse clinical picture and rashes are commoner (Evans, 1960; Hobson *et al.*, 1958; Pejme, 1964).

Little is known for certain about the mode of spread though it is thought to be by the respiratory system. One very intriguing suggestion was made by Hoagland who studied the disease in army cadets in the

* Paper read at the Section of Laryngology, Royal Society of Medicine, March 5th, 1965.

https://doi.org/10.1017/S0022215100065336 Published online by Cambridge University Press

United States and found evidence that one method of transmission from patient to patient was by the intimate mixing and exchange of saliva (Hoagland, 1955).

Evans at Wisconsin University followed this up by designing a questionnaire to try and determine the incidence of kissing among students admitted with glandular fever and a control series with various other illnesses (Evans, 1960). The enquiry covered 60 days preceding the illness and showed a very significant difference in favour of glandular fever being transmitted in this way. What Evans calls "this delightful concept" has apparently achieved some notoriety among the student population at Wisconsin and he reported that "some students view infectious mononucleosis as a socially acceptable mark of romantic achievement".

In describing the clinical features it is customary to divide glandular fever into several types, such as anginose, glandular, typhoidal and sometimes icteric and meningitic, but the picture is so often a mixed one that this does not really serve a useful purpose.

For an acute infection the illness starts relatively slowly and may be preceded by a period of malaise and fatigue, often attributed to overwork. The usual duration of fever is from 3 to 5 days, but it may be longer or even absent altogether. The temperature is usually only moderately raised and seldom exceeds 102°F. Most cases show a late afternoon or early evening rise, and are often first diagnosed as influenza.

Enteric fever may be closely simulated in the early stages. Brucellosis is another possibility in some of these cases, and the diagnosis is made more difficult when, as sometimes happens, there is a transient rise in the Widal and agglutination reaction to Brucella, examples of the anamnestic reaction.

The faucial and palatal appearances and the symptoms associated with them are described elsewhere by Mr. Pickard. The lymphadenopathy which occurs in most cases, always involves the anterior cervical group but these, of course, do not help very much in diagnosis. Enlargement of the posterior cervical and occipital groups is more suggestive. Axillary and inguinal glands may also be involved and a chest X-ray may show hilar lymphadenopathy though this is not usually marked. The glands are always bilateral and never severely painful or tender. They are never hot or red and they never fluctuate or suppurate unless there is a mixed infection. They are commonly visible as well as palpable but are seldom large enough to produce a bull neck.

Serious diseases such as acute leukæmia and Hodgkin's disease may produce similar glands; they affect the same age group and may cause fever and splenomegaly. The blood picture, and, if positive, the Paul Bunnell test distinguish them, though the abnormal cells in glandular fever may cause confusion. Tuberculous adenitis is sometimes suspected. Toxoplasmosis, a benign condition causing lymphadenopathy, may cause

https://doi.org/10.1017/S0022215100065336 Published online by Cambridge University Press

difficulty, and the blood picture often resembles that of glandular fever. Serological tests in toxoplasmosis depend on rising titres and mean a delay of 2 or 3 weeks before a result can be obtained.

The spleen in glandular fever can be felt in about half the cases, but it usually only shows slight or moderate enlargement. Rupture of the spleen is well-recognized, though rare, and is a cause of death in a disease where death is a very unusual outcome. Jaundice occurs in about 8 per cent. but is nearly always mild and harmless, nor does it need the careful management accorded to infective hepatitis. A high proportion of cases of glandular fever without jaundice have a palpable, sometimes tender liver with abnormal liver function tests. Glandular fever is sometimes mistaken for infective hepatitis which itself may be associated with lymphadenopathy and lymphocytosis. Pharyngitis, however, does not occur, nor as a rule is the spleen enlarged.

Characteristic œdema of the eyelids occurs in about a third of the cases. This is often slight and may need the patient's or a relative's opinion to decide whether it is normal or not. Cases like this may be mistaken for angioneurotic œdema, trichiniasis or acute nephritis, but none of these is associated with lymphadenopathy or a lymphocytosis.

The rash is a good deal more common in sero-negative cases and is only seen in 3 per cent. where the Paul Bunnell is positive. It is not of much use in diagnosis as it occurs late, is often short-lived and consists of a non-specific erythema or a pink, rubella-like rash. Much more commonly seen is a drug rash, very often due to sulphonamides. Rubella may cause some difficulty in differential diagnosis as occipital lymphadenopathy is common and there may be a lymphocytosis with abnormal forms. Serum sickness may also cause confusion. Secondary syphilis with rash, glands and a palpable spleen may resemble glandular fever and this may be made more difficult still in the occasional case of glandular fever where the Wassermann reaction becomes transiently positive.

The remaining clinical features are all uncommon. Perhaps the best known is meningitis. Simple headache is common; so is the finding of lymphocytes in the cerebrospinal fluid without headache, but clinical lymphocytic meningitis is rare. Apart from benign lymphocytic meningitis, tuberculous and other forms of meningitis may cause difficulty.

In the central nervous system there has also been described blurred vision, convulsions, stupor, coma, encephalitis and the Guillain-Barré syndrome, the last of these providing another very rare cause of death from respiratory paralysis.

Myocarditis and pneumonitis have both been described and very occasionally are causes of death. Glandular fever may be mistaken for other forms of pneumonia. Albuminuria and microscopic hæmaturia are found occasionally, but chronic renal damage is not to be expected.

Convalescence is very variable, sometimes remarkably rapid once the

https://doi.org/10.1017/S0022215100065336 Published online by Cambridge University Press

temperature has fallen, sometimes very slow with months of debility. There is a relapse rate of 6 per cent., usually in the first few weeks. Later relapses must be looked upon with suspicion, because the abnormal blood picture sometimes remains for many months and the Paul Bunnell may become positive again as a result of a different illness altogether. This is another example of the anamnestic reaction and may account for some of the reports that reticuloses have followed glandular fever, as well as explaining some of the more unusual clinical pictures occasionally ascribed to glandular fever.

There is no specific treatment. ACTH has been reported to give dramatic benefit in one very severe case (Doran *et al.*, 1953), but a controlled trial in a series of routine cases has not shown any benefit (Evans 1960), though in another series it has been suggested that recovery was quicker when the patients were treated with a combination of ACTH and tetracycline (Cronk *et al.*, 1956). ACTH should be reserved for the very severe case. General measures need not include isolation or prolonged or strict rest. Once the diagnosis is made the illness can be looked upon as benign. Symptomatic treatment will be needed for pain and fever.

The hæmatological changes mainly involve the mononuclear leucocytes of the peripheral blood. There is an absolute lymphocytosis which may be considerable—something over 10,000/c.mm. and many atypical cells may be seen. Downey as long ago as 1923 classified these into three types (Downey *et al.*, 1923). These may resemble lymphocytes, lymphoblasts, monocytes or plasma cells but there is no real difficulty in making the distinction. Very early in the disease a polymorphonuclear leucocytosis may occur, which can be very misleading; this may be followed by neutropenia. Occasionally thrombocytopenia is found and this can lead to fatal hæmorrhage. A hæmolytic anæmia has been described with a positive Coomb's test. In the absence of these last two rare events anæmia is not a feature of the illness.

The Paul Bunnell test is now a good deal more sophisticated than it was when it was first introduced. It measures the presence of agglutins in the patient's serum to sheep red cells; these heterophil antibodies may be found in normal people and with serum sickness, as well as in various other diseases. In glandular fever, however, these antibodies are completely absorbed by ox red cells and only partially or not at all absorbed by guinea-pig kidney. This differential test is specific for glandular fever. If clinical and hæmatological glandular fever is all one disease, then about 70 per cent. of cases are sero-positive and their titres, by and large, correspond in timing and quantity to the duration and amount of abnormal mononuclears in the blood. The other way of looking at it is to demand a positive Paul Bunnell test before making the diagnosis and to call the sero-negative cases either a clinical variant of glandular fever or a completely different disease resembling glandular fever. In clinical

https://doi.org/10.1017/S0022215100065336 Published online by Cambridge University Press

practice it may be better to include all the cases because the prognosis and treatment are much the same.

A concept of the disease presented by Evans seems to fit in with the known facts (Evans, 1960). He suggests there are three phases. In the first which occurs mostly in children and often goes unnoticed, there are short-lived respiratory symptoms and transient fever. This phase has a short incubation period of only a few days and may pass into phase 2, the stage of viræmia, where there is fever, adenopathy, often a rash, and mild to moderate lymphocytosis. The Paul Bunnell test is negative in phase 1 and usually in phase 2, though it may be weakly positive. Both these phases occur commonly in childhood. Phase 2 may also include some cases labelled as benign lymphocytosis in children. Phase 3 represents the consequence of tissue reaction with high lymphocytosis, many atypical mononuclears and frequently a high-titre Paul Bunnell. This is the classical disease in the young adult and phases 1 and 2 may go unnoticed. The incubation period of this phase may be as long as 6 weeks.

It is interesting that Pfeiffer's original description of glandular fever in 1889 contained the report of a family where four sibling fell ill in the course of a month with symptoms and signs which would fit in well as examples of these three phases (Pfeiffer, 1889).

REFERENCES

Cronk, G. A. and Naumann, D. E. (1956) *J. Lancet*, **76**, 77.
Davidsohn, I., Stern, K. and Kashiwagi, C. (1951) *Amer. J. clin. Path.*, **21**, 1101.
Doran, J. K. and Weisberger, A. S. (1953) *Ann. intern. med.*, **38**, 1058.
Downey, H. and McKinlay, C. A. (1923) *Arch. inter. Med.*, **32**, 82.
Evans, A. S. (1960) *Amer. J. Hyg.*, **71**, 342.
Hoagland, R. J. (1955) *Amer. J. med. Sci.*, **229**, 262.
Hobson, E. G., Lawson, B. and Wigfield, M. (1958) *Brit. med. J.*, **1**, 845.
Pejme, J. (1964) *Acta. med. scand.*, Suppl. 413.
Pfeiffer, E. (1889) *Jb. Kinderheilk.*, **29**, 257.

Lewisham Hospital,
Lewisham High Street,
London, S.E.13.

https://doi.org/10.1017/S0022215100065336 Published online by Cambridge University Press